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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/008,945	01/20/98	GRIFFITH-CIMA	L 20220-0169

EXAMINER

HM12/0815

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1651	21

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 5/30/00

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-9, 11, 12 + 14-24 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-9, 11, 12 + 14-24 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

The amendment and declaration of 5/30/00 have been entered. The amendment amended claims 1-3, 11, 21 and 22, and added claims 23 and 24.

Claims examined on the merits are 1-9, 11, 12 and 14-24 which are all claims in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to disclose hardening by introducing the cell-polymeric composition into a physiological environment, and adequate for this limitation is not found in the specification.

Claims 1-9, 11, 12 and 14-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and claims dependent thereon are confusing by claim 1 requiring forming a cell-polymeric composition by mixing a solution of polymer, and not being clear as to what the solution of polymer is mixed with. To form a cell-polymeric composition, the solution of polymer would have to be mixed with cells. It is suggested that claim 1 be amended in line 3 by inserting -- dissociated cells with -- after "mixing", and in line 7 canceling "with" and inserting -- containing the --.

Claims 5 and 6 are unclear by requiring the cell-polymeric composition to be hardened whereas claim 1 requires hardening the polymer in line 6. It is suggested that "cell-polymeric composition" in line 1 of claims 5 and 6 be replaced with -- polymer --. Similarly, in claim 9, the polymer rather than the coll-polymeric composition should be hardened. To make this clear, in line 3, before "hardened" insert -- the polymer is --.

Claim 7 is unclear as to where in the method of claim 1 the cell-polymeric composition is further stabilized by cross-linking with multivalent ions, and the meaning and scope of "further stabilized" is uncertain. No stabilization has been required in claim 1, and there is no antecedent basis for being <u>further</u> stabilized. Is being stabilized before or after the hydrogel is formed? In view of the specification (paragraph bridging pages 7 and 8), cross-linking with multivalent ions results in forming the hydrogel. If this is what is intended in claim 7, the claim should be amended by canceling "the cell-polymeric composition is further stabilized" and inserting -- hardening is --, and after "cross-linking" in line 2 insert -- the polymer --. Claim 17 should be similarly amended. If claim 7 is intended to be directed to reacting the hydrogel with polycations or polyanions to a provide the hydrogel with a semi-permeable surface membrane as disclosed in the specification at page 8, lines 18-37, claim 7 should be amended by canceling "cell-polymeric composition is further stabilized by cross-linking with multivalent ions" and inserting -- hydrogel is reacted with polycations or polyanions to provide the hydrogel with a semi-permeable surface membrane --. Claim 17 should be similarly amended.

Claim 11 and claims dependent thereon are unclear by claim 11 requiring a cell-polymeric composition comprising a polymer, and not requiring cells to also be present. It is suggested that claim 11 be amended in line 2 by inserting -- dissociated cells and -- after the colon, and in line 4, canceling "mixed with" and inserting -- containing the --, and in line 5, changing "polymer" to -- polymeric --.

Claim 11 is further unclear as to what is hardened. To make this clear, in line 3, after "hardening" insert -- the polymer --.

To be consistent with the above amendment to claim 11, claim 12 should be amended in line 2 by canceling "cell-polymeric composition" and inserting -- polymer --. Similarly, to be consistent in claims 15 and 16, "cell-polymeric composition can be" (bridging lines 1 and 2) should be replaced with -- polymer is --.

Claim 11 is confusing and unclear as to whether the claimed implant comprises the hydrogel, or the implant comprises the cell-polymeric composition containing the polymer and cells, and the polymer is capable of being hardened to form a hydrogel containing the cells. If the claimed implant is not intended to contain the hydrogel, the claim should be amended by canceling "upon hardening, the implant comprises" in line 3 and inserting -- the polymer is capable of being hardened to form --. If the claim intends the implant to comprise the hydrogel, the claim should be amended in line 3 by canceling "upon hardening, the implant comprises" and inserting -- the polymer is hardened to form --.

In claim 23, the meaning and scope of "physiological environment" is uncertain. The specification fails to recite and define this term.

Furthermore, when an environment is physiological or not physiological is relative and subjective.

Claims 1, 3-8, 11, 14-19, 21, 23 and 24 are rejected under 35 U.S.C. 102(a) as being anticipated by Atala et al (abstract presented at the annual meeting of American Academy of Pediatrics on Oct. 10-15, 1992) (newly applied).

The claims are drawn to a method of introducing cells into an animal to form tissue by introducing into the animal a cell-polymeric composition containing cells and a polymer, and hardening the polymer to form a hydrogel. Also claimed is an implant that is the cell-polymeric composition.

Atala et al disclose mixing a suspension of chondrocytes with alginate, and injecting the resultant chondrocyte/alginate solution with a needle subcutaneously into a mouse where the alginate is gelled and cartilage is formed. The method of Atala et al and the chondrocyte/alginate solution used therein are encompassed by the present claims.

Stating that Alan B. Retik (who is an author) is not an inventor in a 37 C.F.R. 1.132 Declaration does not remove Atala et al as a reference. The present application contains Keith T. Paige as an inventor who is not an author. Even with Retik not being an inventor, the inventive entity of the present invention is different from the authorship of the abstract.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(f) he did not himself invent the subject matter sought to be patented.

Claims 1, 3-8, 11, 12, 14-19, 21, 23 and 24 rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

The Atala et al abstract applied above does not contain Paige as an author whereas Paige is a co-inventor of the claimed invention along with co-inventors Griffith-Cima, Vacanti and Atala who are co-authors of the abstract. Since the abstract discloses a method and implant within the scope of the present claims, the claims encompass subject matter which the present inventive entity did not invent. It is not seen how Paige can be a co-inventor of the method and implant of the abstract along with co-inventors who are co-authors of the abstract, and not be a co-author of the abstract.

Claims 2, 9, 12, 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atala et al (abstract) in view of Nevo et al (4,642,120) and Vacanti et al (5,041,138), and if necessary in further view of Vacanti et al (J. Ped. Surg.).

Claim 2 requires the cell-polymeric composition to be hardened before introduction into an animal, claim 12 requires hardening the composition into a desired anatomical shape and claim 9 requires hardening while the composition is in a mold having a desired anatomical shape. Claims 20 and 22 require the cells to be osteoblasts.

Nevo et al disclose (col 1, lines 5-10 and col 3, lines 62-68) repairing cartilage or bone by implanting a gel containing chondrocytes or bone marrow stem cells .

Vacanti et al ('138) disclose forming a molded matrix containing chondrocytes for implanting to form cartilage (col 3, lines 17-43).

Vacanti et al (J. Ped. Surg.) disclose forming a polymer-cell scaffold for implanting wherein a desired shape of the polymer scaffold may be obtained by solvent casting or compression molding (page 3, right col).

It would have been obvious to gel the chondrocyte-containing alginate solution of Atala et al in a mold to provide a desired shape, and then implant the shaped gel as suggested by Nevo et al implanting a gel containing cells to repair a defect and Vacanti et al ('138), and if needed Vacanti et al (J. Ped. Surg.), disclosing implanting molded scaffolds containing cells. When desiring to repair bone as suggested by Nevo et al, the use of osteoblasts as the cells would have been obvious since these are known bone forming cells.

The comments set forth above in regard to the declaration also apply to this rejection.

Claims 1, 2, 4-8, 11, 14-18, 20 and 22-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Schlameus et al (5,294,446) for reasons set forth in the previous office action of 1/28/00 and reiterated below.

Schlameus et al disclose mixing osteoprogenitor cells with a solution of alginate, gelling the alginate to form microcapsules containing the cells and implanting the microcapsules to regenerate bone (col 3, lines 51-68, and col 4, lines 30-40).

The present claims encompass mixing cells with an alginate solution to form a cell-alginate composition, and gelling the alginate to form microcapsules as disclosed by Schlameus et al.

Applicants urge that Schlameus et al does not disclose an implant that is a hydrogel with dissociated cells as in claim 11, and introducing cells into an animal in which a cell-polymeric composition is hardened as in claim 1.

This argument is unpersuasive since claims 1 and 11 clearly encompass the microcapsules containing cells as disclosed by Schlameus et al. The microcapsules do not contain an alginate solution and cells as asserted by applicants. The microcapsules are formed throughout of alginate gel containing embedded cells. See col 4, lines 36-38, of Schlameus et al. After gelling the alginate, there is no solution in the microcapsules. Claim 1 is not limited to hardening after introducing the cell-polymeric composition into an animal. The claim encompasses hardening before or after introduction into an animal as is apparent from dependent claims 2 and 3.

Claims 3, 5 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlameus et al in view of Barry et al (5,266,326) and Dionne et al (WO 92/19195), and if necessary in further view of Bhatnagar (5,354,736) for reasons set forth in the previous office action, and repeated below.

The claims requires hardening the cell-polymeric composition after introduction into an animal or in a physiological environment.

Schlameus et al is described above.

Berry et al disclose (abstract and col 3, lines 40-45) injecting an alginate solution and a calcium chloride solution into intra-articular space following closure of a surgical site, and allowing the alginate to gel *in situ* to prevent intra-articular adhesions. The alginate solution may contain drugs and other therapeutic agents (col 6, lines 52-55).

Dionne et al disclose (page 4, lines 5-16) forming an implantable vehicle containing cells by immobilizing cells in a hydrogel matrix core and surrounding the core with a jacket or membrane that is permselective and prevents the cells in the core from immunological attack. The core and membrane can be made of the same composition hydrogel (page 9, lines 21-22) and can be alginate cross-linked with calcium ions (page 9, lines 3-6, and page 18, line 10). It is possible for a single, continuous hydrogel matrix to provide both immunoisolation and support or immobilization (page 53, lines 5-24). It is further disclosed (page 18, lines 18-24) that a hydrogel matrix precursor solution can be included but not exposed to polymerizing conditions. In the case of sodium alginate, a hydrogel will form after implantation as calcium ions are scavenged from surrounding tissues.

Bhatnagar discloses (abstract and col 13, lines 45-49) carrying out soft and hard tissue repair by implanting a hydrogel matrix that promotes cell attachment to the matrix and cell migration into the matrix. The hydrogel matrix results in a three dimensional environment that causes cells to differentiate (col 13, lines 50-55). When soft tissue repair is carried out, injection can be prior to gelation and the gel formed in situ (col 13, lines 58-60).

It would have been obvious to omit forming microcapsules and inject the cell-containing alginate solution of Schlameus et al into intra-articular space as suggested by Berry et al to allow *in situ* gel formation to prevent intra-articular adhesions, and as suggested by Dionne et al disclosing forming an alginate hydrogel containing cells after implantation as calcium ions are scavenged from surrounding tissues as an alternative to forming an alginate gel matrix containing cells and implanting the matrix. If needed, further suggestion is provided by Bhatnagar disclosing forming a hydrogel *in situ* for tissue repair. The disclosure by Berry et al that drugs or other therapeutic agents can be in the injected alginate solution would have suggested that the cells of Schlameus et al can be present in the alginate solution when injected to obtain the tissue repair function of the cells in addition to preventing adhesions as disclosed by Berry et al.

Applicants argue that injecting cell-containing alginate into intra-articular space cannot prevent adhesions and repair tissue, and the injection of cells into such space can produce adhesions. However, claim 1 encompasses the cell-polymeric composition being introduced into intra-articular space, and there is inadequate evidence to establish that having cells in the alginate will not prevent adhesions or cause adhesions. The alginate gel formed in the space will function to reduce adhesions irrespective of whether cells are present. Since the cells are in the gel and form specific tissue that is not the fibrinous exudate that causes adhesions, the presence of cells will not cause adhesions.

Claims 9, 12, 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schlameus et al in view of Nevo et al (4,642,120) and

Vacanti et al (5,041,138), and if necessary in further view of Vacanti et al (J. Ped. Surg.) for reasons in the previous office action as repeated below.

Claim 9 requires hardening the cell-polymeric composition in a mold having a desired anatomical shape, and claim 12 requires hardening the cell-polymeric composition into a desired anatomical shape. Claims 19 and 21 require the cells to be chondrocytes.

The references are described above.

It would have been obvious to form the alginate gel of Schlameus et al into a molded anatomical shape instead of microcapsules as suggested by Nevo et al implanting a gel containing cells that is not in the form of microcapsules and by Vacanti et al ('138), and if needed Vacanti et al (J. Ped. Surg.), disclosing implanting molded scaffolds containing cells. Nevo et al and Vacanti et al ('138) use chondrocytes as the cells implanted, and it would have been obvious to implant these cells for their known cartilage forming function.

Applicants' argument in regard to Nevo et al not providing motivation for molding is unpersuasive since the rejection is based on Nevo et al in combination with other references. The Vacanti et al references disclose molded scaffolds for implanting, and would have suggested molding. The motivation for using a molded gel instead of gelled capsules is to obtain the function of the molded gel instead of the capsules. Schlameus et al does not teach that it is critical to use capsules and that other shapes will be inoperative.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone

number is (703) 308-0520. The examiner can normally be reached on Monday-Thursday and every other Friday from about 8:30 AM to about 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, a message can be left on voice mail.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn, can be reached at telephone number (703) 308-4743.

The fax phone number is (703) 305-3014 or 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1657

DMN
8/11/00